[CONTRIBUTION FROM THE RESEARCH DIVISION, SMITH, KLINE, AND FRENCH LABORATORIES AND THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

UNSYMMETRICAL *p,p'*-DISUBSTITUTED DIPHENYLHEXANES RELATED TO HEXESTROL[1]

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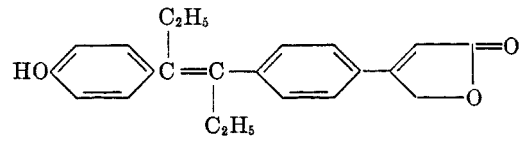
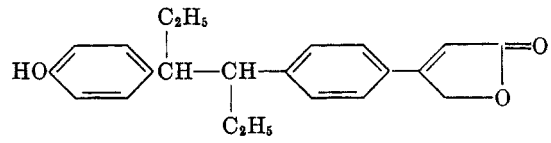
The structural similarity (1) of the remarkably potent synthetic estrogens, diethylstilbestrol and hexestrol, to the naturally occurring steroidal estrogens has prompted a number of attempts (2) to prepare similar synthetic analogs of other medicinally useful steroidal agents. To date, synthetic analogs of progesterone, (2a), desoxycorticosterone (2a, 3), and the cardiac aglycones (4) have been reported. None of these has shown any appreciable activity.

One of the objectives of the present work was the preparation of the two unsaturated lactones, I and II. After the preparation of II had been completed, Campbell and Hunt (4c) reported the synthesis of both I and II, and we abandoned our synthesis of I.



I



II

Another objective of this work was the preparation of certain nitrogen-containing derivatives (5) of 3,4-diphenylhexane in order to investigate whether any of these compounds exhibited pharmacological properties similar to those of the veratrum alkaloids.

The two intermediate phenolic carboxylic acids, VII and VIII, required for this work, were prepared as shown in the Flow Sheet. For purposes of comparison, samples of these acids were also prepared utilizing the procedure of Biggerstaff and Wilds (2a).

The procedure, III–VII, represents no significant improvement over the synthesis of VII (m.p. 143–146° and presumably *trans*) described by Bigger-

[1] This work was taken in part from the dissertation submitted by Lennox B. Turnbull to the University of Virginia in fulfillment of the requirement for the Ph.D. degree, May, 1951.

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staff and Wilds. We were able to separate a crystalline isomer (presumably *trans*) of V (6) in low yield (19%). This crystalline isomer could be converted to the crystalline stilbene acid (VII, m.p. 143–146°), through the crystalline cyano derivative VI in an over-all yield of 66%.

The synthesis, IX–VIII, is based on work described by Brownlee (7) and co-workers and represents a considerable improvement (35% over-all yield) over the methods presently available for the synthesis of VIII. We have confirmed, as have Campbell and Hunt, the unsubstantiated statement of Brownlee and Duffin (7b) that the Friedel-Crafts reaction of chloroacetyl chloride with XII yields the *para* derivative XIII. However, in several other steps, our results do not agree with those of Brownlee and co-workers (7a). They report that the dehydration of X by distillation furnishes a quantitative yield of the crystalline isomer (m.p. 79–80°) of XI. In the dehydrations of X which we carried out, the yields of the crystalline isomer of XI did not exceed 50%. Furthermore, in our hands, hydrogenation of the crystalline isomer of XI never yielded more than 10% of the crystalline isomer of XII, while hydrogenation of non-crystalline XI gave yields of crystalline XII (m.p. 89–90°) as high as 60%.

The chloroketone, XIII, obtained from crystalline XII has been converted to the high-melting isomer of VIII and shown to be identical with a sample of this acid (m.p. 166–168°) prepared by the method of Biggerstaff and Wilds. Thus, all of the derivatives prepared from crystalline chloroketone, XIII, have the same bridge configuration as *meso*-hexestrol.

In a similar fashion, we have shown that the chloroketone, XIII, obtained from non-crystalline XII can be converted to the low-melting isomer of VIII (m.p. 126–128°) described by the same authors.

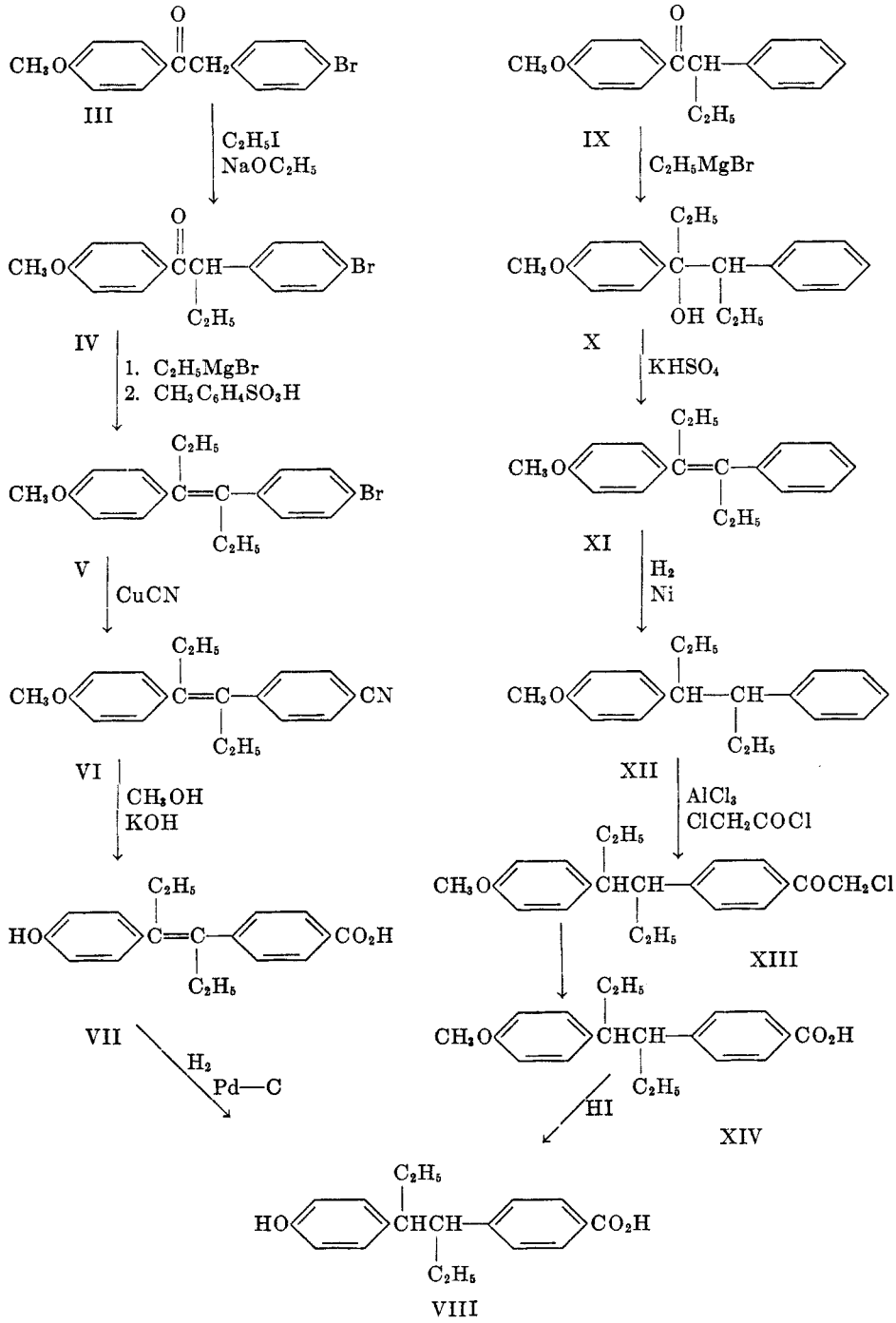
In the synthesis of intermediates necessary for I and II, we have prepared both α,α-diethyl-4′-acetoxy-4-acetoxyacetylstilbene and 3-(*p*-acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)hexane described by Biggerstaff and Wilds. We have also repeated their preparation of 3-(*p*-aminophenyl)-4-(*p*-methoxyphenyl)-hexane and the corresponding hydroxy compound. Our results in larger scale work agree in every regard with those reported by these workers.

We had also completed the synthesis of the derivatives of 3,4-diphenylhexane (high-melting isomer) described by Campbell and Hunt before their publication appeared. Our melting points agreed closely in all but one case with those of these authors. They report a melting point of 136° for 3-(*p*-$\Delta^{\alpha,\beta}$-butenolylphenyl)-4-(*p*-hydroxyphenyl)hexane. Our sample of this compound melted at 147–150° with softening at 138°. It is possible that this discrepancy can be explained by different rates of heating. The synthesis of this compound as well as that of 3-(*p*-bromoacetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)hexane is included in the experimental section.

Pharmacological testing has not yet revealed any interesting properties for these compounds.

Acknowledgement. A portion of the work in this paper was based on ideas and suggestions made by Dr. Arthur E. Heming. The work of one of us (L. B. Turnbull) was supported by a Merck and Company predoctoral Fellowship.

FLOW SHEET


III
C_2H_5I
$NaOC_2H_5$
IV
1. C_2H_5MgBr
2. $CH_3C_6H_4SO_3H$
V
CuCN
VI
CH_3OH
KOH
VII
H_2
Pd—C
VIII
IX
C_2H_5MgBr
X
$KHSO_4$
XI
H_2
Ni
XII
$AlCl_3$
$ClCH_2COCl$
XIII
XIV
HI

EXPERIMENTAL[3]

3-(p-Carboxyphenyl)-4-(p-hydroxyphenyl)hexane. (High-melting isomer). Method A. The procedure of Biggerstaff and Wilds (2a) was repeated. The higher-melting isomer of the phenolic acid melted at 166–168°. The corresponding acetate melted at 174–176°.

Method B. α-(p-Bromophenyl)-p-methoxyacetophenone (III). A solution of 250 g. (1.16 moles) of *p*-bromophenylacetic acid (8) in 170 ml. (2.34 moles) of thionyl chloride was heated at 50° for 2 hours and then at gentle reflux for 2 hours. The excess thionyl chloride was removed *in vacuo* and remaining traces were removed by the successive addition and removal *in vacuo* of two 150-ml. portions of dry benzene. The crude acid chloride was dissolved in a mixture of 550 ml. of anisole and 550 ml. of benzene and to this solution was added with stirring, 400 ml. of anhydrous stannic chloride in 400 ml. of dry benzene. After standing for 16 hours at room temperature, the mixture was hydrolyzed with ice and hydrochloric acid. The white solid which formed was removed, washed with dilute alkali and water, and dried; it weighed 273 g., m.p. 130–132°. The benzene layer was washed with alkali and water, and the benzene and excess anisole were removed by vacuum distillation to yield an additional 60 g., m.p. 134–137°. Crystallization from toluene yielded 251 g. (71%), m.p. 140–141°.

Anal. Calc'd for $C_{15}H_{13}BrO_2$: C, 59.03; H, 4.29.
Found: C, 58.76; H, 4.29.

α-(p-Bromophenyl)-p-methoxybutyrophenone (IV). A solution of 210 g. (0.69 mole) of α-(*p*-bromophenyl)-*p*-methoxyacetophenone in 1000 ml. of dry toluene was added to a solution of 17.5 g. (0.76 mole) of sodium in 1000 ml. of absolute ethanol. After 2 hours of reflux, 133 g. (0.83 mole) of ethyl iodide was added rapidly and reflux was continued for 30 minutes. An additional 3.5 g. (0.15 mole) of sodium in 88 ml. of absolute ethanol and 48 g. (0.3 mole) of ethyl iodide were added and reflux was continued for one hour. The addition of sodium ethoxide and ethyl iodide was repeated and after an additional 6 hours of reflux, the solution was diluted with a large volume of water. The toluene layer was separated and the product was isolated by distillation; the yield was 187 g. (81%), b.p. 180–185° (0.3 mm.).

Anal. Calc'd for $C_{17}H_{17}BrO_2$: C, 61.27; H, 5.14.
Found: C, 61.26; H, 5.11.

4-Bromo-α,α'-diethyl-4'-methoxystilbene (V) (6). The Grignard reagent prepared from 40 g. (0.36 mole) of ethyl bromide and 7.4 g. (0.3 mole) of magnesium turnings in 400 ml. of ether was added with stirring and cooling to a solution of 93 g. (0.28 mole) of α-(*p*-bromophenyl)-*p*-methoxybutyrophenone in 400 ml. of ether. After standing overnight at room temperature, the reaction mixture was decomposed with aqueous ammonium chloride solution and the ether layer was separated and dried. The ether was removed and the residual oil was heated under a water-aspirator vacuum at 130° with 10 g. of *p*-toluenesulfonic acid monohydrate for 90 minutes. The toluenesulfonic acid was removed by extraction with water and the ether solution of this product was distilled. Fraction (a), 56 g., b.p. 152–159° (0.4 mm.), partially crystallized and the solid which formed was separated with ether and crystallized from alcohol; it weighed 18 g. (19%), m.p. 94–95°. Fraction (b), 15 g., b.p. 160–180° (0.4 mm.), was combined with the filtrates from the first fraction and redistilled; this process yielded 33 g., b.p. 160–178° (0.4 mm.). The analytical data refer to the crystalline product.

Anal. Calc'd for $C_{19}H_{21}BrO$: C, 66.09; H, 6.13; Br, 23.15.
Found: C, 66.02; H, 6.06; Br, 23.42.

4-Cyano-α,α'-diethyl-4'-methoxystilbene (VI). A solution of 32 g. (0.09 mole) of the noncrystalline 4-bromo-α,α'-diethyl-4'-methoxystilbene and 12.5 g. (0.14 mole) of cuprous cyanide in 180 ml. of quinoline was heated at reflux temperature for 6 hours. The warm

[3] All melting points are corrected. Microanalyses were carried out by Mrs. Ruth S. McCard, Mrs. Rita Preis, Mrs. Frances Harper, and by the Clark Microanalytical Laboratory, Urbana, Illinois.

solution was then poured cautiously (hood!) into a large excess of cold concentrated hydrochloric acid. The product was extracted into chloroform and purified by distillation; it weighed 20.5 g. (76%), b.p. 163–178° (0.4 mm.).[4]

A 10-g. sample of the crystalline bromo compound when treated as above yielded 6 g. of bromine-free product, m.p. 95–97° after crystallization from alcohol.

Anal. Calc'd for $C_{20}H_{21}NO$: C, 82.43; H, 7.25; H, 4.80.

Found: C, 82.53; H, 7.60; N, 4.74.

When treated with methanolic potassium hydroxide according to the procedure of Biggerstaff and Wilds (2a), the crystalline cyano compound was converted to *α,α'-diethyl-4'-hydroxy-4-stilbenecarboxylic acid* (VII, m.p. 143–146°) in nearly quantitative yield.

The higher-melting isomer of 3-(p-carboxyphenyl)-4-(p-hydroxyphenyl)hexane (VIII). When 25 g. (0.086 mole) of the oily isomer of 4-cyano-α,α'-diethyl-4'-methoxystilbene was treated with methanolic potassium hydroxide, 8 g. (32%) of crystalline α,α'-diethyl-4'-stilbenecarboxylic acid (m.p. 134–137°) and 12 g. of noncrystalline acid were obtained. Hydrogenation of the non-crystalline material yielded 4 g. of the higher-melting isomer of the dihydro acid; m.p. 166–168°. This product was identical with the acid prepared by method *A*.

Method C. p-Methoxy-α-phenylbutyrophenone (IX) (9). This ketone was prepared from 164 g. (1.0 mole) of α-phenylbutyric acid using essentially the same procedure employed in the preparation of α-(*p*-bromophenyl)-*p*-methoxyacetophenone. The product, b.p. 140–144° (0.2 mm.), weighed 233 g. (92%) and melted at 46–48°.

3-(p-Methoxyphenyl)-4-phenyl-3-hexanol (X).[5] A solution of 570 g. (2.24 mole) of *p*-methoxy-α-phenylbutyrophenone in 1000 ml. of ether was added with stirring and cooling to a solution of the Grignard reagent prepared in 1500 ml. of dry ether from 62.4 g. (2.57 moles) of magnesium turnings and 300 g. (2.75 moles) of ethyl bromide. After standing overnight at room temperature, the mixture was cooled and hydrolyzed by the dropwise addition of a cold solution of 300 g. of ammonium chloride in 2000 ml. of water. The ether layer was separated, washed and dried. The ether was then removed and the product distilled to yield 558 g. (88%) of pale yellow oil, b.p. 160–164° (0.8 mm.), $n_D^{23.5}$ 1.5622. Although some dehydration apparently occurred during the distillation, this product was essentially the carbinol as shown by the analytical data.

Anal. Calc'd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51.

Found: C, 80.84; H, 8.27.

α,α'-Diethyl-p-methoxystilbene (XI) (7a).[5] A mixture of 400 g. (1.41 moles) of 3-(*p*-methoxyphenyl)-4-phenyl-3-hexanol and 130 g. of freshly fused and finely pulverized potassium bisulfate was heated at 130–145° (internal temperature) under a water-aspirator vacuum for 30 minutes. The cooled liquid was taken into ether and this solution was washed with aqueous sodium bicarbonate and dried. Removal of the ether *in vacuo* yielded 370 g. of pale yellow oil. Distillation of a small portion gave a product, b.p. 124–130° (0.3 mm.), n_D^{24} 1.5652. This distillate did not crystallize on long standing and when a small sample was dissolved in an equal volume of petroleum ether and seeded with the crystalline high-melting isomer (m.p. 79–80°) only a trace of crystalline product formed.

In other dehydrations using *p*-toluenesulfonic acid, yields of crystalline isomer (m.p. 79–80°) as high as 50% were realized.

3-(p-Methoxyphenyl)-4-phenylhexane (High-melting isomer of XII) (7a).[5] A solution

[4] Neher and Miescher [*Helv. Chim. Acta*, **29**, 449 (1946)] report b.p. 170–174° (0.8 mm.) for this compound.

[5] Brownlee and coworkers (ref. 7a) mention 3-(*p*-methoxyphenyl)-4-phenyl-3-hexanol but do not describe its preparation. According to their data, this carbinol, when distilled at 325–330°, undergoes dehydration to give a quantitative yield of crystalline α,α'-diethyl-4-methoxystilbene, m.p. 79–80°. They also report that hydrogenation of the methoxystilbene compound (presumably the crystalline compound m.p. 79–80°) gives a nearly quantitative yield of the high-melting isomer of 3-(*p*-methoxyphenyl)-4-phenylhexane (m.p. 89–90°).

of 175 g. (0.66 mole) of α,α'-diethyl-*p*-methoxystilbene (crude liquid isomer above) in 750 ml. of ethyl acetate containing 40 g. of Raney nickel catalyst was hydrogenated (10) at 2200 p.s.i. and room temperature for 3 hours and then at 100° for an additional 3 hours. The uptake of hydrogen corresponded to 100% of theory. After removal of the catalyst and solvent, the product was crystallized from petroleum ether; it weighed 108 g. (61%), and melted at 87.5–89.5°. Concentration of the filtrate yielded 68 g. of an oil which could not be crystallized. It distilled at 131–141° (0.5 mm.); n_D^{25} 1.5475.

Hydrogenation of the crystalline stilbene isomer under a variety of conditions invariably gave non-crystalline products.

The high-melting isomer of *3-(p-hydroxyphenyl)-4-phenylhexane* (7a) was obtained by refluxing the methyl ether with a mixture of glacial acetic acid and hydriodic acid (*sp. gr.* 1.70). After recrystallization from benzene-petroleum ether, it melted at 140–141.5°.

3-(p-Chloroacetylphenyl)-4-(p-methoxyphenyl)hexane (High-melting isomer of XIII) (7b). A solution of 94.6 g. (0.35 mole) of 3-(*p*-methoxyphenyl)-4-phenylhexane (m.p. 87.5–89.5°) in 400 ml. of carbon disulfide was added dropwise with stirring to a mixture of 117 g. (0.88 mole) of anhydrous aluminum chloride and 59.5 g. (0.53 mole) of chloroacetyl chloride in 330 ml. of carbon disulfide. The mixture was stirred at reflux temperature for one hour, cooled, and poured into cracked ice containing 175 ml. of concentrated hydrochloric acid. One liter of chloroform was added and the non-aqueous phase was separated, washed and dried. Removal of the solvent under reduced pressure gave a white solid which was crystallized from isopropyl alcohol; it weighed 96.5 g. (80%), m.p. 137–139.5°. Several crystallizations of a small sample from methanol yielded a white crystalline product, m.p. 146–147°.

Anal. Calc'd for $C_{21}H_{25}ClO_2$: C, 73.13; H, 7.31.

Found: C, 73.03; H, 7.54.

The chloroketone (6 g.) was heated at reflux temperature for 6 hours with a mixture of 75 ml. of glacial acetic acid and 60 ml. of hydriodic acid (*sp. gr.* 1.70). The *3-(p-acetylphenyl)-4-(p-hydroxyphenyl)hexane* (2a) which formed was crystallized from toluene; the yield was 2.5 g. (37%), m.p. 154–156°.

Anal. Calc'd for $C_{20}H_{24}O_2$: C, 81.06; H, 8.16.

Found: C, 80.92; H, 8.22.

3-(p-Carboxyphenyl)-4-(p-methoxyphenyl)hexane (High-melting isomer of XIV) (2a). A solution of 21 g. (0.06 mole) of 3-(*p*-chloroacetylphenyl)-4-(*p*-methoxyphenyl)hexane in 225 ml. of dioxane was added at 55° with good stirring to 700 ml. of dilute potassium hypochlorite solution (1.1 moles). The rate of addition was so adjusted that the temperature did not rise above 64°. After stirring at 60° for 30 minutes, the solution was cooled to 10° and a solution of 25 g. of sodium bisulfite in 100 ml. of water was added. The product was isolated by acidification with hydrochloric acid and purified by crystallization from 85% acetic acid; the yield was 16 g. (85%), m.p. 167–169°.

3-(p-Carboxyphenyl)-4-(p-hydroxyphenyl)hexane (High-melting isomer of VIII). A solution of 14 g. (0.045 mole) of 3-(*p*-carboxyphenyl)-4-(*p*-methoxyphenyl)hexane in a mixture of 150 ml. of glacial acetic acid and 200 ml. of hydriodic acid (*sp. gr.* 1.70) was heated at reflux temperature for 5 hours. The solution was poured into 1000 ml. of water and the product was crystallized from benzene; 12 g. (90%), m.p. 167–168°. It did not depress the melting point of a sample of this acid prepared according to the procedure of Biggerstaff and Wilds.

The *acetate*, prepared in glacial acetic acid using pyridine and acetyl chloride melted at 174–175°, after crystallization from benzene-petroleum ether. It likewise did not depress the melting point of a sample of the acetate prepared according to the procedure of Biggerstaff and Wilds.

3-(p-Dimethylaminoacetylphenyl)-4-(p-methoxyphenyl)hexane hydrochloride. A mixture of 9 g. (0.03 mole) of 3-(*p*-chloroacetylphenyl)-4-(*p*-methoxyphenyl)hexane (m.p. 137–140°) and 7.7 g. (0.17 mole) of dimethylamine in 50 ml. of dioxane was heated in a pressure bomb at 70° for 3 hours. The dioxane was removed *in vacuo* and the residue was taken up in ether and extracted with water. The ether solution was dried and acidified with hydrogen chloride.

The hydrochloride was crystallized from ethanol-ether and weighed 2.5 g. (21%), m.p. 198–200°.

Anal. Calc'd for $C_{23}H_{32}ClNO_2$: C, 70.84; H, 8.27; Cl^-, 9.09.

Found: C, 70.61; H, 8.27; Cl^-, 9.00.

3-(p-Piperidinoacetylphenyl)-4-(p-methoxyphenyl)hexane hydrochloride. A solution of 9 g. (0.026 mole) of 3-(*p*-chloroacetylphenyl)-4-(*p*-methoxyphenyl)hexane (m.p. 137–140°) in 150 ml. of dry benzene was heated at reflux temperature for 6 hours with 4.45 g. (0.052 mole) of piperidine. The piperidine hydrochloride was removed and the benzene solution was washed with water and extracted with dilute hydrochloric acid. The hydrochloride crystallized in this process. It was removed and recrystallized from ethanol-ether; the yield was 2.0 g. (18%), m.p. 228–230°.

Anal. Calc'd for $C_{26}H_{36}ClNO_2$: C, 72.62; H, 8.44; Cl^-, 8.25.

Found: C, 72.58; H, 8.73; Cl^-, 8.20.

3-(p-N-Piperidinophenyl)-4-(p-methoxyphenyl)hexane. A solution of 8 g. of 3-(*p*-aminophenyl)-4-(*p*-methoxyphenyl)hexane (m.p. 103–104°) (2a), 5.12 g. of pentamethylene iodide, and 2.72 g. of sodium acetate in 40 ml. of 95% ethanol was refluxed for five hours. The solvent was removed *in vacuo* and the crystalline residue was continuously ether extracted from a Soxhlet thimble for six hours. After removing the ether, the solid residue was recrystallized from 95% ethanol to yield 3.5 g. of colorless crystalline solid, m.p. 115–117°.

Anal. Calc'd for $C_{24}H_{33}NO$: C, 82.00; H, 9.46; Mol. wt., 351.

Found: C, 81.40; H, 9.09; Mol. wt. (cryoscopic method in benzene), 342.

3-(p-N-Piperidinophenyl)-4-(p-hydroxyphenyl)hexane. A solution of 1.0 g. of 3-(*p*-N-piperidinophenyl)-4-(*p*-methoxyphenyl)hexane in a mixture of 10 ml. of acetic acid and 10 ml. of 48% hydrobromic acid containing one drop of 50% hypophosphorous acid was refluxed for four hours. The hydrobromide salt which separated on cooling overnight was crystallized from ethanol; m.p. 250–255°. It was converted to the free base which was crystallized from a mixture of benzene and petroleum ether and weighed 0.9 g., m.p. 162–163.5°.

Anal. Calc'd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26.

Found: C, 81.85; H, 9.03.

3-(p-N-Pyrrolidinophenyl)-4-(p-methoxyphenyl)hexane. This compound was prepared from 7.5 g. of 3-(*p*-aminophenyl)-4-(*p*-methoxyphenyl)hexane (m.p. 103–104°) and tetramethylene iodide by essentially the same procedure described for the piperidino analog. After crystallization from ethanol 3.0 g. of colorless crystals, m.p. 128–130° was obtained.

Anal. Calc'd for $C_{23}H_{31}NO$: C, 81.85; H, 9.26.

Found: C, 82.02; H, 8.98.

3-(p-N-Pyrrolidinophenyl)-4-(p-hydroxyphenyl)hexane. This compound was prepared from 2.0 g. of 3-(*p*-aminophenyl)-4-(*p*-hydroxyphenyl)hexane (m.p. 185–189°) (2a), 1.27 g. of tetramethylene iodide, 0.67 g. of sodium acetate, and 15 ml. of ethanol using the procedure described for the methyl ether. The crude product (0.65 g.) after repeated crystallization from dilute ethanol melted at 134–140°.

Anal. Calc'd for $C_{22}H_{29}NO$: C, 81.68; H, 9.04.

Found: C, 81.67; H, 8.74.

3-(4-Hydroxy-6-quinaldyl)-4-(p-methoxyphenyl)hexane. A solution of 20 g. of 3-(*p*-aminophenyl)-4-(*p*-methoxyphenyl)hexane (m.p. 103–104°) in a mixture of 10 g. of ethyl acetoacetate and 80 ml. of methanol was refluxed overnight. The solvent was removed by distillation and the residual oil was added to 150 ml. of boiling diphenyl ether. After refluxing for 15 minutes, the solution was cooled and diluted with petroleum ether. The crude brown product (3 g.) was repeatedly crystallized from methyl *tert*-butyl ketone; m.p. 237–238°.

Anal. Calc'd for $C_{23}H_{27}NO_2$: C, 79.04; H, 7.79.

Found: C, 78.54; H, 8.26.

Ethyl 3-(p-hydroxyphenyl)hexane-4-[p-(β-anilinocrotonate)]. A mixture of 4.0 g. of 3-(*p*-aminophenyl)-4-(*p*-hydroxyphenyl)hexane (m.p. 185–189°) and 4 ml. of ethyl acetoacetate was warmed on the steam-bath to effect solution. One drop of dilute hydrochloric acid was added and the solution was placed in the vacuum desiccator overnight. Crystallization

of the solid mass from benzene-petroleum ether gave 3.5 g. of colorless product, m.p. 123–125°.

Anal. Calc'd for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67.
Found: C, 75.96; H, 8.04; N, 3.81.

3-(p-Hydroxyphenyl)-4-(4-hydroxy-6-quinaldyl)hexane. A total of 3.1 g. of ethyl 3-(4-hydroxyphenyl)hexane-4-[p-(β-anilinocrotonate)] was added in portions to 30 ml. of boiling diphenyl ether. The mixture was heated and stirred for 20 minutes, cooled to room temperature, and diluted with petroleum ether. The crude product (2.6 g.) after crystallization from ethylene glycol melted at 350–353°.

Anal. Calc'd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51.
Found: C, 78.75; H, 7.41.

3-(p-$\Delta^{\alpha,\beta}$-Butenolylphenyl)-4-(p-hydroxyphenyl)hexane (4c). To a solution of 3.7 g. (0.01 mole) of 3-(*p*-acetoxyacetylphenyl)-4-(*p*-methoxyphenyl)hexane (m.p. 94–95°) in 60 cc. of dry dioxane was added 2.0 g. (0.3 mole) of clean, 20 mesh zinc, 0.001 g. of iodine, and 2.0 g. of freshly distilled ethyl bromoacetate. The mixture was stirred well and heated to reflux. At 15-minute intervals for 1.5 hours, reflux was interrupted, 0.5-g. portions of fresh zinc were added and after 45 minutes, an additional 1.0 g. of ethyl bromoacetate was added. After standing overnight, the mixture was poured into a mixture of 200 g. of cracked ice and 200 ml. of dilute hydrochloric acid. The sticky solid was extracted into ether and this solution was washed with water and aqueous bicarbonate. The ether was removed and the solid (3.0 g.) was dissolved in 60 ml. of glacial acetic acid saturated with dry hydrogen bromide. This dark solution was heated at reflux for 1.5 hours and then 12 ml. of aqueous 48% hydrobromic acid and 1 drop of hypophosphorous acid were added and reflux was continued for 1.6 hours. The dark solution was cooled to 30° and poured with stirring into 200 g. of cracked ice. The gray solid was removed by filtration, washed well with water, and dried. Crystallization from alcohol and then dioxane-ether gave 0.5 g. (15%) of a white crystalline product, m.p. 146–150°. A third crystallization from dioxane-ether gave 0.4 g.; m.p. 147–150° with some softening at 138°. This material gave a strongly positive Legal test.

Anal. Calc'd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19.
Found: C, 77.79; H, 7.21.

The *acetyl* derivative was prepared by refluxing 0.3 g. of this material with 5 ml. of acetic anhydride for four hours. The resulting solution was poured into cracked ice and allowed to stand for six hours. The solid was crystallized from a mixture of ethanol and toluene; it weighed 0.17 g.; m.p. 168–170°.

Anal. Calc'd for $C_{24}H_{26}O_4$: C, 76.17; H, 6.90.
Found: C, 76.45; H, 6.79.

3-(p-Acetoxyphenyl)-4-(p-bromoacetoxyacetylphenyl)hexane. To a solution of 21 g. (0.057 mole) of 3-(*p*-acetoxyphenyl)-4-(*p*-diazoacetylphenyl)hexane (2a) (m.p. 131–133°) in 175 cc. of warm toluene was added a solution of 33.4 g. (0.24 mole) of bromoacetic acid in 50 ml. of dry toluene. The resulting red mixture was heated at 90–100° for one hour. A small amount of insoluble material was then removed by filtration and the filtrate was extracted with five 150-ml. portions of water. The toluene solution was dried and the solvent was removed by distillation *in vacuo*. The residual viscous red oil was dissolved in acetone and decolorized. The solution was then diluted with 500 ml. of water and the sticky oil which formed was extracted into ether. After washing with water, the ether solution was dried and the ether was removed *in vacuo*. Crystallization of the residual material from methanol and then from benzene-petroleum ether gave 11.0 g. (38%) of yellow crystalline product, m.p. 122–123°.

Anal. Calc'd for $C_{24}H_{27}BrO_5$: C, 60.63; H, 5.73.
Found: C, 60.57; H, 5.59.

3-(p-Carboxyphenyl)-4-(p-hydroxyphenyl)hexane (*Low-melting form of* VIII). *Preparation and hypochlorite oxidation of non-crystalline 3-(p-chloroacetylphenyl)-4-(p-methoxyphenyl)hexane.* A total of 100 g. of the non-crystalline 3-(*p*-methoxyphenyl)-4-phenylhexane (b.p. 131–141°/0.5 mm.) was treated with chloroacetyl chloride and aluminum chloride in

the same manner described for the crystalline isomer. The product was extracted into chloroform and this solution was washed well and dried. Removal of the chloroform yielded 114 g. of light red oil.

This oil was oxidized in aqueous dioxane with dilute sodium hypochlorite solution using the same procedure described for the oxidation of crystalline 3-(*p*-chloroacetylphenyl)-4-(*p*-methoxyphenyl)hexane. In this case, however, sufficient heat was generated in the oxidation reaction to bring the temperature to 90° and to cause some ring chlorination. By extraction with ether and crystallization from 90% acetic acid, 40 g. of a crystalline monochloro acid, m.p. 176–179° was obtained.

Anal. Calc'd for $C_{20}H_{23}ClO_3$: C, 69.25; H, 6.68.
Found: C, 69.18; H, 6.50.

3-(p-Carboxyphenyl)-4-(p-methoxyphenyl)hexane (*Low-melting isomer of* XIV). A solution of 0.5 g. of the chloro acid above in 25 ml. of 95% ethanol containing 2.0 g. of 10% palladium on charcoal and 1 ml. of 10% potassium hydroxide solution was hydrogenated at room temperature and 40 p.s.i. for 12 hours. After removing the catalyst and solvent, the product was taken up in water and isolated by acidification. After several crystallizations from ethanol, it weighed 0.40 g. and melted at 165–168°. This melting point was depressed 30° by admixture with a sample of the isomeric acid, m.p. 167–169°.

Anal. Calc'd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74.
Found: C, 77.16; H, 7.86.

3-(p-Carboxyphenyl)-4-(p-acetoxyphenyl)hexane (*Low-melting isomer*) (2a). A solution of 1.5 g. of the monochlorinated derivative of 3-(*p*-carboxyphenyl)-4-(*p*-methoxyphenyl)-hexane in a mixture of 18 ml. of acetic acid and 9 ml. of 48% hydrobromic acid containing one drop of 50% hypophosphorous acid was heated at reflux temperature for six hours. This solution was poured into water. The viscous oil which separated solidified upon standing and was crystallized from a benzene-isooctane mixture; it weighed 1.0 g., m.p. 146–152°.

The chlorine was catalytically removed from 0.5 g. of the above compound as previously described to yield 0.3 g. of product which, after crystallization from benzene and isooctane and drying *in vacuo*, softened at 80° and melted at 120–125°.

The *acetyl* derivative was prepared in glacial acetic acid using acetyl chloride and pyridine. After crystallization from dilute alcohol, it melted at 130–132°. A mixture melting point[6] with a sample of the acetyl derivative (m.p. 129–133°) prepared by Biggerstaff and Wilds showed no depression.

Anal. Calc'd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11.
Found: C, 73.90; H, 6.88.

SUMMARY

3-(*p*-Carboxyphenyl)-4-(*p*-methoxyphenyl)hexane and the corresponding hydroxy analog are useful intermediates for the synthesis of unsymmetrical compounds related to *meso*-hexestrol. Several methods of preparing these intermediates have been investigated and an improved synthesis is described. A number of new basic derivatives (both heterocyclic and open chain) have been prepared from these intermediates.

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[6] Kindly determined by Professor A. L. Wilds of the University of Wisconsin.

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